SYNOPSYS

Synthesis, Chemistry and Biological Evaluation of Some Pyrimido pyrimidine Compounds and it's Derivatives.

Shortly Resume Of The Plan Proposed for Investigation for Ph.D. Degree Under the Faculty of Science.

To Be Submitted to

SWAMI RAMANAND TIRTH MARATHWADA UNIVERSITY, NANDED

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Thesis Tital

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INTRODUCTION

Amongst all heterocyclic compounds, pyrimidine exhibits broad spectrum of biological activities as of its occurrence in deoxyribonucleic acid (DNA) bases; cytosine, thymine, and uracil. The basic skeleton of pyrimidine is also present in vitamin B1 and barbiturates. Pyrimidine derivatives also used as hypnotics, such as veranal. The bioactive moiety pyrimidine has a voluminous therapeutic profile as it is a vital component of a series of natural composites and chemotherapeutic drugs. Since from last 50 to 60 years, this motif has been used commendably against bacterial, tuberculosis viral, malarial, fungal, and cancerous contagions . Recently, numerous pyrimidine derivatives were synthesized and discussed here, fused with other heterocyclic moieties, pyrazole, coumarine, triazole, alkenyloxindole, hydrazine, and others, were also investigated for their bioactivities.

Pyrimidine an organic aromatic heterocyclic compound, is chemically analogous to pyridine and benzene. Six- membered ring having one or two nitrogen atoms are known as azine or pyridine , and diazine respectively, e.g., pyridazine , pyrimidine , and pyrazine . [3,4] Pyridazine, pyrimidine, and pyrazine are known as 1, 2, 1, 3, and 1, 4 diazines, respectively. Cytosine, thymine and uracil , are the nitrogenous bases (pyrimidine analogue) found in nucleic acid. Pyrimidine is a crystalline, water soluble and colorless solid having bitter smell with molecular mass 80.088 g cm−3. Its melting and boiling point are 22 and 123–124 °C.

Pyrimidine having hydroxyl , mercapto , and amino groups at 2, 4, and 6 position is tautomeric with their oxo , thio , and imino group respectively. It is verified from literature that, pyrimidine derivatives have been synthesized using classical methods, green chemistry routes, microwave synthesis, and various others. These protocols are of importance because of high yield, low reaction time and eco-friendly synthesis.

Fused pyrano[2,3-d]pyrimidine derivatives have been prepared in the presence of 1,4 diazabicyclo[2,2,2]octane (DABCO), base catalyst . The application of DABCO catalyst in organic reactions increases gradually due to use of less noxious solvent, eco-friendly procedures and give high yield in minimum time. By irradiating the chemicals with microwaves, aryl sulfonyl pyrimidine compounds were synthesized . Reaction facilitated through microwaves affords maximum yield (95%) in less time as associated to conventional method. A multicomponent reaction, using urea , ethyl acetoacetate , and aryl aldehyde , is Biginelli reaction, yield dihydropyrimidine , the most common method for the formulation of active pyrimidine derivatives.

Molecules Introduction :

Phytopathogenic fungi that easily infect many crops are hard to control and risk resistance to the widely used commercial fungicides , therefore, there is a continuous need for new classes of antifungal agents. Natural compounds containing pyrimidine skeletons, such as vitamin B1 ,

and nucleotide bases play an important role in life science studies. Pyrimidine derivatives have attracted great interest due to their diverse biological activities. Pyrimidine derivatives have also occupied a prominent place in the field of agrochemicals because of their significant properties as fungicides in agriculture. To date, some important commercial pyrimidine fungicides, such as azoxystrobin, cyprodinil, pyrimethanil,and diflumetorim .

Eleven novel pyrimidine derivatives of three classes had been synthesized and identified. The bioactivity tests showed that most of them had antifungal activities. The antifungal activities of most of compounds were equal to or higher than those of the commercial fungicides flumorph and dimethomorph. Compounds 3b, 4b and 4c showed better activity than the lead compound, pyrimethanil to GF. Compound 3b was more potent to AM than pyrimethanil. Compounds 1a and 3b displayed certain broad-spectrum activity towards the tested fungi. Compounds 4a, 4b, 4c and 4d showed relatively moderate antifungal activity. The preliminary SAR can offer great help to design more active compounds as potent fungicides.

Natural occurrence Therapeutically important agents, heterocyclic scaffolds, have wide existence in nature. Substituted pyrimidines isolated and synthesized from nature; plants, animals, microorganisms, and marines, use as a synthon for drug designing. Hydrolysis of bovine thymus, calf thymus and herring sperm leads to pyrimidine bases; thymine , cytosine , and uracil isolation respectively. Plants have been used as basis for the extraction, isolation, and synthesis of pyrimidine composites. Nucleic acid fractions from plant materials, such as bracken fern, clover, ryegrass whole leaves, and sugar beet tops are used for the separation of pyrimidine. Betaine (N,N,N-trimethylglycine), compound enclosing quaternary nitrogen, present in plant (sugar beet), use against homocystinura, homocystenemia, and cardiovascular diseases. To exploit its more pharmacological effects heterocyclic mesoionic pyrimidinium betaines have been synthesized and reported. The desired compound can be synthesized using derivatives of esters and pyridine . Aromatic organic compound 4-methoxy-7-methyl-furo[3,2-g]chromen-5-one existing in Ammi visnagen plant seeds and fruits are called khellin and visnagen , used in treatment of angina and kidney stone, used as photochemotherapeutic, phototherapeutic, and anti-inflammatory agents.

Conclusion : Pyrimidine is the most important heterocyclic diazine, possessing potent biological applications. Electrophilic substitution reaction at 2, 4, and 6 position of the ring takes place in the presence of electron realizing group. Pyrimidine derivatives are prepared using different methods and provide enormous scope in medicinal chemistry, by showing potent anticancer, antifungal, anti-inflammatory, antibacterial, and antiviral activities. Thus, commercially it would be very important in pharmaceutical industry and act as backbone in drugs due to their biological activities.

Literature Survey : A literature survey identified several pyrimidine derivatives in the development phase as potential new drugs. The versatility of the pyrimidine in addition to its relative chemical simplicity and accessibility, makes these chemicals amongst the most promising sources of bioactive compounds. Biologically active molecules that contain heterocyclic rings has play important roles in the drug discovery process and exhibit various biological activitie

The present survey has clearly demonstrated that pyrimidine may be successfully used to synthesize a wide variety of heterocycles of academic and

[4,3d]pyrimidines and screened them for antiinflammatory, analgesic and antipyretic pharmaceutical intetest .

- Min low and Dequn sun et al synthesized antifungal activity of some pyrimidine derivatives.
- Mohamed A. Abdelgawad reported synthesis and antibacterial evolution of new azo- pyrimidine derivatives.
- Lotfi shirin et al in 2017 reported synthesis of pyrono[2,3,d] pyrimidine under green chemistry.
- Kategaonkar et al, reported ionic liquid catalyzed multicomponent synthesis of 3,4-dihydro-3substituted-2H-naphtho[2,1-e][1,3]oxazine derivatives from 1-naphthol, various anilines and formalin at room temperature stirring. The sixmembered N,O- heterocyclic skeleton was constructed via 1-benzyl-3-methyl imidazolium hydrogen sulphate [bnmim] [HSO4] promoted Mannich type reaction.
- Hitchings et,al, made an important observation that a large number of 2, 4-diamino pyrimidines and some 2- amino- 4 hydroxypyrimidines are antagonists of folic acid.
- Futterman S. et,al eventually proved that these pyrimidines were inhibitors of the enzyme dihydrofolatereductase (DHFR).
- Cheng CC et,al showed that 2, 4-diaminopyrimidine drugs, pyrimethamine is a selective inhibitor of the DHFR of malarial plasmodia and trimethoprim, an antibacterial drug is also a selective inhibitor and selectively inhibits bacterial DHFR.

Objectives :

Specific objectives of our current research program include the synthesis of novel pyrimido pyrimidine their derivatives.

- One pot synthesis of amino pyrimidine using ethyl cyno acetate and guanidine nitrate , thiourea and urea.
- Reaction of amino pyrimidine nucleus with Michael accepter to give pyrimido pyrimidine.
- Reaction of pyrimido pyrimidine nucleus with various aromatic phenols.
- Reaction of pyrimido pyrimidine nucleus with various aromatic amines.
- Reaction of pyrimido pyrimidine nucleus with various hetryl amines.
- Reaction of pyrimido pyrimidine nucleus with various different hydrazines.

- ❖ Pharmacological activity of above synthesized compounds.

Methodology:

By known synthetic method synthesis of amino pyrimidine , amino thiazine and amino oxazine. The synthesized amino pyrimidine , amino thiazine and amino oxazine is act as a Michael donars and it condence with Michael acceptar to give pyrimido pyrimidine,pyrimido thiazine and pyrimidooxazine .

Pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine act as a electrophillic species condence with various nucleophile such as aromatic amines, aromatic phenols, hetryl amines and also cyclise with some different hydrazine and biological evaluation of above synthesized compounds.

International status:

Since from the last three decades, we have witnessed the revolutionary synthesis pyrimido pyrimidine,pyrimido thiazine and pyrimidooxazine of many researchers throughout the world. Although there are huge number of articles on pyrimidopyrimidine ,pyrimido thiazine and pyrimidooxazine.

1) Hanadi A. Katouah et al (2019) synthesized and Docking study of pyrimidine derivatives scaffold for anti hypertension applications.
2) Cenicola and Co-workers evaluated some imidazolopyrimidines for antiinflammatory, analgesic and antipyretic activities. Anti-inflammatory activity was studied by carrageenan- induced paw oedema in rats and found to show activity comparable to indomethacin.
3) Abdullah's Al-bogani synthesized antimicrobial activity possessing a trifluoro methyl moiety.
4) FumiyoshiIshikawa, and Co-workers synthesized cyclic Guanidines derivatives and then screened them for blood platelet aggregation inhibitors activity.
5) FarhatJubeen and co-workers gives review on Eco-friendly synthesis of pyrimidines and its derivatives.

6) Ahmed Hamza and Co-workers synthesized Some New Triazine, 1, 3-Oxazine, Fused Pyridine and Pyrimidine Derivatives with their antibacterial activity.
7) Tatyana Anikova et al in July 2017 synthesized compounds of the pyrimidine series based on the reaction of 3-Aryl methyl idene furan 2 (3H)-ones with N,N-Binucleophhilic reagent.
8) ZainabAmer and Co-workers: synthesized some thiazine and pyrazole derivatives by using chalcones. In this study, chalcones were synthesised by condensing 2acetylpyridine with aromatic aldehyde derivatives in dilute ethanolic potassium hydroxide solution at room temperature. Thiazine and Pyrazole were synthesized by reaction between chalcones with thiourea and urea respectively.
9) FarhadHatamjafari and Co-workers give Synthesis of 1,2-Dihydro-1 arylnaphtho [1,2-e] [1,3] oxazine-3-ones using nano-Fe2O3 as an acid catalyst and solvent-free conditions .

National Status :

Apart from the international contribution some of the Indian researchers have also made their mark on synthesis of pyrimido pyrimidine , pyrimido thiazine and pyrimidooxazine.

1) Chetan M. Bhalgat et al in 2010 gives novel pyrimidine and its derivative. Synthesis and investigation of antioxidant and anti-inflammatory activity.
2) Mohammad Asif in 2017 studied on chemistry and biological potential of pyrimidine derivatives: study of nucleoside with pyrimidine.
3) Vanita Sharma et al in 2014 studied on significance of biological importance of pyrimidine in microbial world.
4) Mallesha lingappa synthesized some new pyrimidine, azitidinone analogous and their antioxidant, in vitro antimicrobial, and antitubercular activity.
5) Bahekar et, alreported the synthesis of some [2-amino-6-(4-substituted aryl)-4-(4substituted phenyl)-1,6-dihydropyrimidin-5yl]acetic acid derivatives and evaluated for anti-inflammatory activity. Only few of them showed remarkable anti-inflammatory activity.

6) Mishra et.al. synthesized various derivatives of pyrimidines. The fungicidal activities of the compound were evaluated against P. infestans and C. falcatum by the usual agar plate technique at 1000, 100 and 10 ppm concentration.

Regional status :

1) Sambhaji P. vartale, Vijay N.Bhosale ,Sandeep V. Khansole and ramdas N. Katapalle (2009) . A convenient one pot synthesis of 3-cyno-9-methyl-2-methylthio-4-oxo-4H-pyrimidi-[2,1-b][4,5-b]quinoline and its reaction with selected nucleophiles. Letters in organic chemistry Vol.6,No7,544-548.
2) Raghunath B.Toche et al in 2016 reported new simple route for the synthesis of pyrimido [1,2-a] pyrimidine derivatives
3) A.H. Kategaonkaret,al give Microwave assisted synthesis of pyrimido[4,5d]pyrimidine derivatives in dry media .
4) Baheti KG, Jadhav JS, Suryawanshi AT and Kuberkar SV (2005) Novel synthesis and antibacterial activity of 15-iminobenzothiazole[2,3b] pyrimido [5,6e] pyrimido[2,3]benzothiazole-14-H ones and its 3,10 disubstituted derivatives. Ind J Chem 44B: 834D
5) Pingle MS, Vartale SP, Bhosale VN and Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2- methylthio-*4H*pyrimido [2,1-*b*] [1,3] benzothiazole and its reactions with selected nucleophilesArkivoc X, 190D.

Scope of the study :

Lot of research work is going on all over the world to investigate organic compounds which will act as effective medicines as anti-HIV, anti-Cancer and anti-tuberculsotatic drug Antibacterial. National Institutes of Health, National Cancer Institute, Bethesda, Maryland, USA showed keen interest in evaluation of such compounds. It is surmised that some newly synthesized compounds mentioned in our proposal using green solventsand these synthesized compounds would exhibit properties required for effective drugs. Synthesis and screening of newly synthesized compounds would lead to the formation of pharmacological importance.

Proposed work plan with tentative chapter scheme

Year	Quarters (Periods of three months)	Milestones
Year I	1 st Quarter	Reference Work
	2nd Quarter	Topic first literature survey
	3rd Quarter	Topic second Experimental Work and characterization
	4th Quarter	Topic second Experimental Work and characterization
Year II	1 st Quarter	Topic third Experimental Work and
	2nd Quarter	Topic third Experimental Work and characterization
	3rd Quarter	Topic Fourth Experimental Work and characterization
	4th Quarter	Topic Fourth Experimental Work and characterization
Year III	1 st Quarter	Topic Fifth Experimental Work and characterization
	2nd Quarter	Topic sixth Biological evaluation
	3rd Quarter	Topic sixth Biological evaluation
	4th Quarter	Writing and typing of the research work and submission of the research work

Expected Outcome :

It is planned to synthesis fused heterocycles using unconventional solvents i.e. bio degradable solvents in good yields and synthesized compounds are expected to show good biological activity.

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